Val or absent; B is Ala, Gly, Val, Ser or absent; C is Ser, Thr or absent; D is Ser, Thr, Ans, Glu, Arg, Ile, Leu or absent; E is Ser, Thr, Asp or absent; F is Thr, Ser, Asn, Gln, Lys, Trp or absent; G is Tyr or absent; H is Thr, Gly, Met, Met(O), Cys, Thr or Gly; and II is Cys, an amide group, substituted amide group, an ester group or absent, wherein said peptide comprises at least 4 amino acids and physiologically acceptable salts thereof.

52. The method of claim 40 wherein the second compound comprises a peptide selected from FVFLM (SEQUENCE ID NO. 1), FVYLI (SEQUENCE ID NO. 16), or mixtures thereof.

REMARKS

Claims 1-45 were originally pending in the subject application. In response to a restriction requirement, claims 1-39 and 43-45 were withdrawn from consideration, without prejudice or disclaimer. New claim 46 was added in the response dated June 5, 2002. Claim 41 is withdrawn from consideration without prejudice or disclaimer, as the Examiner states that the claim does not encompass the elected species. Claims 40, 42 and 46 are amended, and new claims 47-52 are added in the instant response to more particularly point out and distinctly claim the subject matter that Applicant regards as their invention. Therefore, the claims now under consideration are 40, 42 and 46-52, as set forth herein. These claims are supported by the specification as filed, and Applicant believes that no new matter has been added. Applicant respectfully requests that the Examiner reconsider and withdraw the various grounds of rejection of the claims.

I. Rejections Under 35 § 112, first paragraph

Claims 40 and 42 are rejected under 35 U.S.C 112, first paragraph as being based on a disclosure that is not enabling. Specifically, the Examiner states that the Applicant's *in vitro* experiments do not enable a method of treating HIV infections in humans.

In accordance with the Examiner's suggestion, Applicant has deleted the term "therapeutically effective" from independent claim 40, upon which claim 42 depends, thereby rendering this objection moot. Applicant thanks the Examiner for his suggested

claim language. Applicant believes that this amendment addresses the Examiner's concerns under 35 U.S.C. 112, first paragraph.

Further, Applicant submits that by these contentions, the Examiner is apparently maintaining his requirement that Applicant demonstrate clinical efficacy of the claimed methods in order to overcome the outstanding enablement rejection. Indeed, Examiner seems to be requiring 100 percent efficacy, certainly a higher threshold than that required by the FDA. Applicant wishes to remind the Examiner, however, that there is no requirement for clinical data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. In fact, the disclosure of in vitro and/or animal testing results has been held to enable claims to in vivo therapeutic compositions and methods of their use. To this end, the Federal Circuit has stated that:

> In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985) Under Cross, one of ordinary skill would thus recognize that the in vitro results described in the present specification "are generally predictive of in vivo test results", Cross, 753 F.2d at 1050, and thus would have a reasonable expectation that the claimed methods would be successful for the claimed in vivo therapeutic approaches.

Applicant notes that at the time of the invention, there was no recognized animal model for HIV. (Indeed, even at the present time, there remains no recognized animal model for HIV.) Applicant has set forth results from three *in vitro* models; U1 cells, PBMC, and MAGI cells. In particular, Applicant also directs the Examiner's attention to the whole blood experiments set forth in Figure 13 as well as the text corresponding thereto. Individuals skilled in the art recognize that these models closely relate to the *in vivo* situation. This is further supported by the commercial and clinical success of existing, publicly available anti-HIV drugs (listed in Example 6), which were all initially

tested in similar *in vitro* models. The results from such models are highly and invariably predictable of the success or failure in clinical setting. Lastly, Applicant directs the Examiner's attention to Shapiro et al., "Alpha-1-antitrypsin inhibits human immunodeficiency virus type 1," FASEB Journal (15) Jan. 2001.

Applicant notes that the Examiner cites to a study by Binquet where patients were treated with HIV protease inhibitors. However, these patients were treated with aspartyl proteases; that is, viral aspartyl inhibitors, whereas the present invention concerns serine protease inhibitors. Further, Applicant draws the Examiner's attention to an article by Hayes et al, entitled "The Genetics of Susceptibility of HIV/AIDS: how Does Africa Differ?" (enclosed herein.) Not only does this article refer favorably to Applicant's work, but further studies are being based upon the findings set forth in the application presently under consideration. See for example: "Novel candidate: *AAT* (alpha-1-antitrypsin) Hypothesis: Alpha-1-antitrypsin inhibits HIV-1 replication (Shapiro et al., 2001), therefore, genetic variation in gene encoding for this protease inhibitor may have an effect on disease progression." at Page 3.

Reconsideration of the rejection and withdrawal thereof is respectfully requested.

III. Rejections Under 35 § 112, second paragraph

The Examiner has rejected claims 40, 42, and 46 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In response, Applicant has amended claims 40 and 42 to read: "[...]exhibiting α_1-antitrypsin (AAT) or AAT-like activity, [...]wherein said compound exhibiting AAT-like activity is a natural or man made molecule that, upon administration to a patient in need thereof, inhibits serine protease[...]"; thus defining the term "compound exhibiting AAT-like activity" to read as a natural or man made molecule that inhibits serine protease. Applicant believes that this amendment resolves any indefiniteness or vagueness that may have existed in the prior claim.

Regarding claim 42, the Examiner states that trademark names are used in the claims. The Examiner states that these names may be used if accompanied by the full names of the compound that they represent. Applicant notes that the claim as amended refers to the generic names. For the Examiner's convenience, Applicant has prepared the following table:

Generic Name	Brand Name	Ownership
saquinavir; aka Ro 31-8959	INVIRASE; FORTOVASE	Roche
ritonavir; aka ABT-538	NORVIR	Abbott
indinavir	CRIXIVAN	Merck
nelfinavir; aka AG1343	VIRACEPT	Agouron/Japan Tobacco
amprenavir; aka VX-478	AGENERASE	Vertex/Kissel/Glaxo Wellcome
KNI-272; aka kynostatin 272		Nikko Kyodo Co.
lasinavir; aka CGP-61755		Ciba/Norvatis
lopinavir; aka ABT-378	ALUVIRAN	Abbott

Applicant has amended the claims to more particularly point out and distinctly claim the subject matter, which Applicant regards as the invention. Applicant believes that these amendments and the remarks provided herein address the Examiner's concerns under 35 U.S.C. 112, second paragraph. Reconsideration of the rejection and withdrawal thereof is respectfully requested.

IV. Rejections Under 35 § 103

On page 6 of the Office Action, the Examiner rejected claim 40 under 35 U.S.C. 103(a) as being unpatentable over Lezdey. Applicant directs the Examiner to page 9, lines 21 to page 10, line 7 of the specification, wherein the background of the invention is described:

> The anti-HIV effect of AAT as speculated by Lezdey et al., (U.S. Pat. No. 5,532,215, incorporated herein by reference in its entirety) was also not confirmed by actual experimental studies carried out by practitioners in the art. Two separate studies, one conducted by Anderson et al., (J Biol Chem, 268(33):24887-91 (1996); and other by Vollenweider et al., (Biochem J, 314 (Pt 2):521-32) (1996), have convincingly demonstrated

> that naturally occurring or non-mutated AAT directed against its natural substrate, elastase, has not shown any anti-HIV activity. Similarly Harvima et al., have shown that putative tryptase receptors on T lymphocytes were not reactive with anti human anti-tryptase antibody (Harvima et al., "*Separation and partial characterization of proteinases with substrate specificity for basic amino acids from human MOLT-4 T lymphocytes: identification of those inhibited by variable-loop-V3 peptides of HIV-1 (human immunodeficiency virus-1) envelope glycoprotein*", Biochem J, 292 (Pt 3):711-8) (1993). Furthermore, Meylan et al., stated that AAT natural substrates such as trypsin, factor Xa, and mast cell tryptase did not enhance the HIV infectivity (Meylan et al., "*HIV infectivity is not augmented by treatment with trypsin, Factor Xa or human mast-cell tryptase*", AIDS, 6(1):128-30) (1992).
> Page 9 Line 21 to Page 10 Line 7.

The Examiner has asked Applicant to describe with particularity the portions of the above cited references by Anderson and Vollenweider, that teach away for Lezdey. Applicant directs the Examiner to Figure 4 of Anderson and the text relating thereto. (Figure 4F illustrates inhibition of HIV replication, while figure 4D does not, even though 4D was coinfected with VV:α_1-NAT (natural AAT)). Relating to the Vollenweider article, Applicant directs the Examiner to pages 530-531.

Thus, Lezdey must be reviewed with an eye to the many references that teach away from the present invention. Further, due to the size of antitrypsin, (molecular weight 51,000) it does not enter the cell. Thus, all activity must occur outside the cell. Only an **antitrypsin like** agent can actually enter the cell due to its smaller size. (See claim 40, claim 46, and dependent claims 47-48 directed to a man-made or natural agent that has a molecular weight of less than 20,000, and upon administration to a patient in need thereof, inhibits serine protease.) Lezdey neither teaches nor suggests the use of these mimics.

Further Applicant submits that Lezdey is frankly not enabling. Indeed, many statements set forth in Lezdey are scientifically not possible. For example, Lezdey states:

- "It is an object of the invention to kill viruses on contact utilizing serine protease inhibitor[...]";

- "It is a further object of the present invention to inhibit proteolytic cleavage of gag-pol precursor proteins of viruses utilizing serine protease inhibitors[...]";
- "[...the inhibitors provide multiple actions [...] inactivating the virus by binding to the core protein of the virus[...]";
- "[...the inhibitors provide multiple actions [...] binding to enzymes which my be available as host sites for viral infiltration"; and
- "serine protease inhibitors of the invention will maintain their viral killing activity even after binding with their natural proteases since the active anti-viral sites on the inhibitor molecule are still free to bind with or kill the virus."

In addition, Applicant draws the Examiner's attention to Example VI of Lezdey, wherein the results were certainly affected by the addition of iodine to the mixture.

On page 7 of the Office Action, the Examiner rejected claim 40 under 35 U.S.C. 103(a) as being unpatentable over Eisenberg. In response, Applicant has expressly excluded SLPI from the claims. Further, Applicant encloses herein an article by Turpin et al., entitled "Human immunodeficiency virus type-1 (HIV-1) replication is unaffected by human secretory leukocyte protease inhibitor" which states that "SLPI did not exert anti-HIV activity under any experimental conditions, and mechanistic studies showed SLPI to have no inhibitory activity on HIV-1 binding, reverse transcriptase or protease." Applicant also encloses an article by McNeely, Shugars, Rosendahl, Tucker, **Eisenberg**, and Wahl, entitled: Inhibition of Human Immunodeficiency Virus Type 1 Infectivity by Secretory Leukocyte Protease Inhibitor Occurs Prior to Viral Reverse Transcription." This abstract states: "SLPI consists of two domains, of which the C-terminal domain contains the protease inhibiting region. However, when tested independently neither domain had potent anti-HIV activity. SLPI binding neither prevented virus binding to monocytes nor attenuated the infectivity of any virus progeny that escaped inhibition by SLPI." Applicant notes that the Dr. Eisenberg that is the co-author of the enclosed article, is the same Dr. Eisenberg listed as the inventor of US Patent No. 6,017,880

Further, Eisenberg (6,017,880) neither teaches nor suggests the use of mimics; e.g. antitrypsin like agents that can actually enter the cell due to their smaller size.

Thus neither Lezdey nor Eisenberg, either alone or in combination, either teaches or suggests the use of antitrypsin like agents. Further, neither Lezdey nor Eisenberg, either alone or in combination, teaches the use of antitrypsin or antitrypsin like agents in combination with HIV reverse transcriptase inhibitors and/or HIV protease inhibitors for inhibition of HIV.

In view of the foregoing amendments and remarks, it is believed that this application is in condition for allowance. A notice to this effect is respectfully requested.

AUTHORIZATION

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment to Deposit Account No. 50-1710.

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CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and withdraws them. There being no other objections or rejections, Applicant respectfully requests that the present application be allowed and pass to issue.

Should any further questions arise concerning this application, the Examiner is invited to call Applicant's attorney at the number listed below.

Respectfully submitted,

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Enclosures:

Hayes et al, *The Genetics of Susceptibility of HIV/AIDS: how Does Africa Differ?*, in press.
McNeely, et al., *Inhibition of Human Immunodeficiency Virus Type 1 Infectivity by Secretory Leukocyte Protease Inhibitor Occurs Prior to Viral Reverse Transcription*, Blood Col 90, No.3 (1997) 1141-1149.
Turpin et al., *Human immunodeficiency virus type-1 (HIV-1) replication is unaffected by human secretory leukocyte protease inhibitor*, Antiviral Research 29 (1996) 269-277.
Geiben-Lynn et al., *Purification of a Modified Form of Bovine Antithrombin III as a Human Immunodeficiency Virus Type 1 (HIV-1) CD8_+ T-cell Antiviral Factor (CAF)*, The American Society for Biochemistry and Molecular Biology, In Press.
Shapiro et al., *Alpha-1-antitrypsin inhibits human immunodeficiency virus type 1*, FASEB Journal (15) Jan. 2001

APPENDIX

MARKED-UP VERSION TO SHOW CHANGES MADE

The claims are amended as follows:

40. A method for inhibiting human immunodeficiency virus (HIV) replication in a patient harboring said HIV comprising administering to the patient a [therapeutically effective] combination comprising:

at least one first compound exhibiting α_1-antitrypsin (AAT) or AAT-like activity, wherein said compound exhibiting AAT-like activity is a natural or man-made molecule that, upon administration to a patient in need thereof, inhibits serine protease, with the exception that the first compound is not serine leukocyte protease inhibitor; and

at least one second compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors, for a time and under conditions effective to inhibit HIV replication.

42. The method according to claim 40 wherein at least one HIV protease inhibitor is saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, [VX-478,] KNI-272, [CGP-61755] lasinavir, or lopinavir [U-103017].

46. A method of inhibiting human immunodeficiency virus (HIV) replication comprising administering to a patient in need thereof, a combination of at least one compound exhibiting α_1-antitrypsin (AAT) or AAT-like activity and one or more compounds selected from a group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors, for a time and under conditions effective to inhibit HIV replication, wherein said compound exhibiting AAT-like activity is a natural or man-made molecule that, upon administration to a patient in need thereof, inhibits serine protease, and with the exception that the compound exhibiting α_1-antitrypsin activity is not serine leukocyte protease inhibitor.

The new claims are as follows:

47. The method of claim 40, wherein said first compound is a man-made molecule.

48. The method of claim 40, wherein said first compound has a molecular weight less

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49. The method of claim 40 wherein the first compound comprises a peptide including at least five amino acid residues comprising the C-terminal sequences of mammalian AAT, analogues of such a peptide, or homologues thereof.

50. The method of claim 40 wherein the first compound comprises a peptide selected from FVFAM (SEQUENCE ID NO. 2), FVALM (SEQUENCE ID NO. 3), FVFLA (SEQUENCE ID NO. 4), FLVFI (SEQUENCE ID NO. 5), FLMII (SEQUENCE ID NO. 6), FLFVL (SEQUENCE ID NO. 7), FLFVV (SEQUENCE ID NO. 8), FLFLI (SEQUENCE ID NO. 9), FLFFI (SEQUENCE ID NO. 10), FLMFI (SEQUENCE ID NO. 11), FMLLI (SEQUENCE ID NO. 12), FIIMI (SEQUENCE ID NO. 13), FLFCI (SEQUENCE ID NO. 14), FLFAV (SEQUENCE ID NO. 15), FAFLM (SEQUENCE ID NO. 17), AVFLM (SEQUENCE ID NO. 18), or mixtures thereof.

51. The method of claim 40 wherein the first compound is represented by a peptide of a general formula (I): I-A-B-C-D-E-F-G-H-II, wherein I is Cys or absent; A is Ala, Gly, Val or absent; B is Ala, Gly, Val, Ser or absent; C is Ser, Thr or absent; D is Ser, Thr, Ans, Glu, Arg, Ile, Leu or absent; E is Ser, Thr, Asp or absent; F is Thr, Ser, Asn, Gln, Lys, Trp or absent; G is Tyr or absent; H is Thr, Gly, Met, Met(O), Cys, Thr or Gly; and II is Cys, an amide group, substituted amide group, an ester group or absent, wherein said peptide comprises at least 4 amino acids and physiologically acceptable salts thereof.

52. The method of claim 40 wherein the second compound comprises a peptide selected from FVFLM (SEQUENCE ID NO. 1), FVYLI (SEQUENCE ID NO. 16), or mixtures thereof.

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